genzyme

GENZYME CORPORATION
ONE KENDALL SQUARE
CAMBRIDGE, MA 02139-1562, U.S.A.
617-252-7500
FAX 617-252-7600

September 10, 1999

The Dockets Management Branch (HFA-305)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Docket # 99N-0193

To Whom It May Concern:

This letter provides Genzyme Corporation's comments on the proposed changes to 21 CFR 314.70 that were published in the Federal Register on June 28, 1999. An electronic copy of these comments has also been submitted to the docket (sagern@cder.fda.gov).

Genzyme appreciates the opportunity to comment on this proposed rule. Should you have any questions concerning these comments, please do not hesitate to call Kimberlee Raymer, Principal Associate, at 508-271-3951.

Sincerely,

David Schubert
Director
Regulatory Affairs
Genzyme Corporation

Kimberlee Raymer
Principal Associate
Regulatory Affairs
Genzyme Corporation

99N-0193

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Genzyme Corporation's Comments on Proposed Changes to 21 CFR 314.70

General Comments:

The phrase "validate the effect of the change" should be replaced with the phrase "assess the effect of the change" throughout the proposed rule. The term "validate" may be misinterpreted to mean cGMP validation.

Genzyme proposes that changes to specifications be categorized and reported as follows:

Major change: drug substance, drug product, intermediates (requires supplement submission and prior approval prior to distribution of the product)

Moderate change: raw materials, container/closure system (requires supplement submission at least 30 days prior to distribution of the product)

Minor change: reagents, in-process materials, all compendial changes (may be described in an annual report)

Specific Comments:

314.70(a)(1)	It is stated that "an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application and that the notice is required to describe the change fully." This statement should be clarified as this requirement could be overly burdensome from the standpoint that some changes, e.g. changes made to batch records submitted as part of the application may not require reporting under CFR 314.70.
314.70 (a)(2)	Replace the phrase "validate the effects of the change" with the phrase "assess the effects of the change".
314.70(a)(6)	While there is no objection to listing all changes, the requirement to do so in a cover letter is overly restrictive. Alternatively, changes could be described at the beginning of the CMC section of the annual report, for instance, using a separate page for this purpose.
314.70(b)(3)(vi)	The requirement that relevant validation protocols be provided in addition to requirements in 314.70(b)(3)(iv) and (b)(3)(v) is overly restrictive and burdensome. We suggest that this statement be rephrased to state "validation protocols may be requested by the FDA".
314.70(c)(2)(ii)	The exclusion of recombinant DNA-derived products is overly burdensome and does not provide for increased comfort as additional experience is gained with these products. These types of products should not be excluded if the change is supported by appropriate validation data.
314.70(d)(2)(i)	Delete the phrase "... and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or represented to possess."

Genzyme Corporation's Comments on Proposed Changes to 21 CFR 314.70, continued

Specific Comments, continued:

314.70(d)(3)(i)	Change the phrase "... effects of the change have been validated" to "... effects of the change have been assessed".
314.70(d)(3)(iii)	The requirement to include "... cross reference to relevant validation protocols and/or SOPs..." is overly burdensome. The listing of this information could be extremely difficult since in some cases, changes could affect a great number of documents.

SPM31

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Company GENZYME CORPORATION

Address 1 KENDALL SQ

Dept./Floor/Suite/Room

City CAMBRIDGE State MA ZIP 02139

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